

Letter of Amendment #1 for:
IMPAACT 2010
Phase III Study of the Virologic Efficacy and Safety of
Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy
Regimens in HIV-1-Infected Pregnant Women and their Infants

Version 2.0, dated 8 December 2017

DAIDS Study ID #30129
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Letter of Amendment Date: 20 July 2018

TABLE OF CONTENTS

Information/Instructions to Study Sites from the Division of AIDS	2
Letter of Amendment Signature Page	3
Summary of Modifications and Rationale	4
Implementation	4
Updates of Abbreviations and Acronyms	4
Updates of Protocol Team Roster	4
Updates of Section 1, Introduction	5
Updates of Section 2, Objectives	6
Updates of Section 4, Study Population	7
Updates of Section 5, Study Drug Considerations	8
Updates of Section 6, Study Visits and Procedures	8
Updates of Section 7, Safety Assessment, Monitoring, and Reporting	14
Updates of Section 8, Participant Management	15
Updates of Section 9, Statistical Considerations	18
Updates of Section 12, Human Subjects Protections	18
Updates of Section 15, References	18
Updates of Appendix I, Schedule of Evaluations	19
Updates of Appendix III, Sample Informed Consent Form	19
Updates of Appendix V, Sample Informed Consent Form for Use of Study Drug during Subsequent Pregnancy	22
Appendix I Schedule of Evaluations	24

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2010 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. Study sites may request expedited review of this LoA and revised site-specific informed consent forms. However, each review body should determine the review procedure to be followed, according to its policies and procedures; all applicable IRB/EC and regulatory entity requirements must be followed.

Before this LoA can be implemented at any site, an “Implementation Notice” for the LoA must be issued by the IMPAACT Operations Center confirming that all operational requirements for implementing the LoA at the network level have been completed. Sites should also follow the instructions below regarding site-specific timing of implementation of the LoA:

For sites that were activated to initiate the study prior to issuance of this LoA:

- Upon obtaining all required IRB/EC and regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.
- Participant accrual may be resumed upon receipt of all required IRB/EC and regulatory entity approvals of protocol Version 2.0 and this LoA, using revised site-specific ICFs corresponding to this LoA.
- For mother-infant pairs enrolled prior to implementation of this LoA, re-consent for study participation should be obtained at the next scheduled study visit, using the revised site-specific ICFs corresponding to this LoA.

For sites that were not activated to initiate the study prior to issuance of this LoA:

- Upon obtaining all required IRB/EC and regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS PRO at the RSC. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete.
- Activation will occur following receipt of all required IRB/EC and regulatory entity approvals for protocol Version 2.0 and this LoA; receipt of a protocol registration notification for protocol Version 2.0; receipt of the protocol registration notification for this LoA; completion of all other study activation requirements; and receipt of a site-specific study activation notice from the IMPAACT Operations Center.

Please file this LoA, corresponding site-specific informed consent forms, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2010. If the IMPAACT 2010 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT 2010
Phase III Study of the Virologic Efficacy and Safety of
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Regimens in HIV-1-Infected Pregnant Women and their Infants

DAIDS Study ID #30129

Version 2.0, Letter of Amendment #1
Letter of Amendment Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record

Date

Name of Investigator of Record
(printed)

Summary of Modifications and Rationale

The main purpose of this LoA is to update the IMPAACT 2010 protocol and sample informed consent forms in response to a recent report of a potential increased risk of neural tube defects (NTDs) associated with exposure to dolutegravir (DTG) at the time of conception. The recent report was based on a preliminary unplanned analysis of data from an observational surveillance study of birth outcomes conducted in Botswana. As explained in protocol text below, these findings are not of immediate concern for mother-infant pairs entering the IMPAACT 2010, as DTG is initiated in the study at or after 14 weeks gestation, well after neural tube formation has occurred. The findings are of potential concern, however, in the event of subsequent pregnancies that enrolled mothers may conceive while taking DTG. Protocol modifications are incorporated to inform site investigators and study participants and to mitigate against the potential increased risk of NTDs in subsequent pregnancies. Modifications are also incorporated to enable exploration of potential mechanisms of action that may lead to NTDs.

This LoA also harmonizes expedited adverse event (EAE) reporting requirements for all study participants, regardless of random assignment or maternal antiretroviral treatment (ART) regimen, as recommended by the Data and Safety Monitoring Board that oversees the study, and incorporates minor corrections and clarifications of protocol text.

Implementation

Modifications of protocol text are presented below, generally in order of appearance in the protocol. where applicable, modified text is showing using strikethrough for deletions and bold type for additions.

Updates of Abbreviations and Acronyms

1. In the listing of abbreviations and acronyms, the following terms are added:

IUD	intrauterine device
IUS	intrauterine system
NTD	neural tube defect

Updates of Protocol Team Roster

2. In the protocol team roster, the following Protocol Investigator is added:

Chelsea Morroni, MD
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Botswana Harvard AIDS Institute Partnership
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Updates of Section 1, Introduction

3. In Section 1.1, Background, fourth paragraph:

DTG, a once-daily integrase inhibitor, is highly efficacious and generally well tolerated. It appears to have a very high barrier to development of HIV drug resistance. In a head-to-head study comparing DTG combined with ABC and 3TC to EFV/FTC/TDF, the DTG combination had superior virologic activity at 48 weeks (described below) (12). **A Cochrane review comparing DTG plus two nucleoside reverse transcriptase inhibitors (NRTIs) to EFV plus two NRTIs concluded that DTG-containing regimens were superior to EFV-containing regimens at 48 and 96 weeks with regard to efficacy, and were associated with reductions in treatment discontinuation (12a). The authors recommended that DTG-based regimens should be considered in future WHO guidelines for initial HIV treatment, and the PEPFAR program has been supporting this recommendation. As of early 2018, more than two dozen countries had changed their guidelines to include DTG in their preferred initial treatment regimen, with 50 additional countries planning to make this change soon (12b, 12c).** DTG is included in two of the preferred first-line regimens recommended for adults by the US DHHS (13) and is used with increasing frequency in well-resourced settings. DTG was also recently included in WHO guidelines as an alternative first-line agent in non-pregnant adults (3) and is being incorporated into new national program guidelines for first-line use in some resource-limited countries. In 2015, CHAI, UNAIDS, and UNITAID announced a new agreement under which generically-manufactured DTG will be available for \$44 /patient per year (a price that is comparable to that of EFV) (14). Hence, it is expected that DTG may soon become a cornerstone of preferred first-line ART treatment globally. **However, further data regarding the safety of DTG in pregnancy, and the safety and efficacy of DTG with concomitant tuberculosis treatment, are awaited prior to recommendation for and adoption of use of DTG more widely.**

4. In Section 1.1, Background, seventh paragraph:

In sum, it is very likely that both DTG and TAF will be used with increasing frequency in the future, potentially as components of first-line recommended ART globally. The WHO 2015 guidelines update noted that neither DTG nor TAF had been studied in pregnancy (both were pregnancy Category B); however, as described in Sections 1.2.2 and 1.3.2, data from studies in pregnancy are emerging. If DTG and TAF are included in future WHO-recommended first-line regimens in resource-limited settings as anticipated, it will be important to have data regarding their efficacy and safety in pregnancy ~~(given the~~ **because of both an ethical imperative to offer pregnant women optimal ART regimens when possible and a desire to use the same first-line ART regimens in pregnant and non-pregnant patients, for programmatic simplicity**~~). These data will also be of relevance in the US and other well-resourced settings.~~

5. In Section 1.2.2, Dolutegravir: Studies in Pregnancy, fifth (added), sixth (added), seventh (added), and eighth paragraphs:

To date, the largest body of data related to birth outcomes following use of DTG in pregnancy is from the Tsepamo birth outcomes surveillance study conducted in Botswana. This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to EFV from conception. Botswana's HIV program moved to universal ART with DTG+FTC/TDF provided as the first-line regimen for patients starting ART, including pregnant women, in May 2016 (women already on other regimens were not switched to a DTG-containing regimen). The previous first-line regimen was EFV/FTC/TDF. Almost all

women on DTG-based and EFV-based ART took these drugs in combination with FTC/TDF. More than 95% of women in Botswana deliver in-hospital, and obstetric records are available for more than 99% of women. The Tsepamo study is conducted at eight of the largest public maternity wards across Botswana, representing approximately 45% of all births in the country. Research assistants abstract exposure data from maternity cards for all consecutive in-hospital deliveries. Trained nurse midwives perform systematic infant surface examinations of all newborns, whether stillborn or live born. Reports and photographs (when available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information. (27a-27c)

A preliminary unscheduled analysis of Tsepamo study data collected between 15 August 2014 and 1 May 2018 was recently performed at the request of colleagues who were preparing for a WHO meeting. This analysis identified four infants with NTDs born to 426 women who became pregnant while taking DTG (prevalence 0.94%, 95% CI 0.37%, 2.4%). In comparison, 14 infants with NTDs were born to 11,300 women who became pregnant while taking a non-DTG-containing three-drug ART regimen (prevalence 0.12%, 95% CI 0.07%, 0.21%); approximately half of these women were taking an EFV-containing regimen). No NTDs were identified among infants born to 2,812 women who started DTG-containing ART during pregnancy (including 280 women who started DTG-containing ART during the first trimester). (27d)

At this time, only a small amount of additional data exists regarding birth outcomes among women taking DTG from conception, from multiple sources of varying data quality and completeness; from these sources, only one NTD was reported among infants born to approximately 323 women taking DTG from conception (27e). Additional data will continue to be collected — in Botswana and ideally in other settings — to try to determine whether this signal for NTDs with DTG exposure from conception persists, and whether it is found in different populations. The mechanisms underlying this NTD finding (if confirmed) are unknown; lower maternal folate levels, maternal diabetes, and maternal obesity are among the known risk factors for NTDs (27f, 27g).

~~An observational surveillance study of birth outcomes in women starting ART during pregnancy (in the context of the national HIV treatment program)~~ The Tsepamo study had previously showed similar rates of **other** adverse pregnancy outcomes (stillbirth, neonatal death, preterm or very preterm birth, small for gestational age or very small for gestational age) among 845 women initiating DTG/TDF/FTC (at median 19 weeks gestation) compared with 4593 women initiating EFV/TDF/FTC (at median 21 weeks gestation) in pregnancy. Among 512 women initiating ART in the first trimester of pregnancy (116 DTG/TDF/FTC, 396 EFV/TDF/FTC), one major congenital abnormality was identified (skeletal dysplasia in an EFV-exposed infant). (28)

Updates of Section 2, Objectives

6. In Section 2.3, Exploratory Objectives:

2.3.7 Assess potential markers of NTDs and the association of these markers with maternal ART regimens

This update is also incorporated into the protocol Schema (edits not shown).

Updates of Section 4, Study Population

7. In Section 4.1, Inclusion Criterion 4.1.2, last paragraph:

At least one sample should be tested using a test that can distinguish HIV-1 from HIV-2. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory setting that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a CLIA-certified (for US sites) or VQA-certified (for non-US sites) laboratory. For tests performed in other settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available. FDA-approved testing methods should be used when possible.

8. In Section 4.1, Inclusion Criterion 4.1.8 (added):

4.1.8 At study entry, mother reports that she does not wish to become pregnant again for at least 50 weeks after her current pregnancy and that she is willing to use effective contraception during this period

Effective contraception may include surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy) or any of the following methods:

- **Contraceptive intrauterine device (IUD) or intrauterine system (IUS)**
- **Subdermal contraceptive implant**
- **Progestogen injections**
- **Progestogen only oral contraceptive pills**
- **Combined estrogen and progestogen oral contraceptive pills**
- **Percutaneous contraceptive patches**
- **Contraceptive vaginal rings**

Note: IUDs, IUSs, implants, and injections are strongly recommended due to their lower failure rates with typical use. Male or female condom use is recommended with all contraceptive methods for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections.

9. In Section 4.2, Exclusion Criterion 4.2.4, ninth bullet point:

- **Clinically significant acute illness requiring systemic treatment and/or hospitalization (i.e., major medical condition that is likely to lead to hospitalization and/or to an adverse pregnancy outcome) within 14 days prior to study entry**

10. In Section 4.2, Exclusion Criterion 4.2.4, note (added at end of criterion):

Note: Testing to rule out HIV-2 infection is not required.

Updates of Section 5, Study Drug Considerations

11. In Section 5.8.1, Maternal Concomitant Medications, IMPORTANT INTERACTIONS WITH HORMONAL CONTRACEPTIVES, added:

IMPORTANT INTERACTIONS WITH HORMONAL CONTRACEPTIVES

Participants will be counseled to use effective contraception postpartum (see Section 8.6).

Higher contraceptive failure rates have been observed for combined oral contraceptives and for progestin-containing subdermal implants when is used in combination with EFV (122a). Mothers taking EFV should be advised to use alternative forms of contraception or to use condoms in combination with oral contraceptives and with progestin-subdermal implants.

Data on interactions between DTG and hormonal contraceptives are limited. DTG does not lead to significant cytochrome P450 (CYP) inhibition or induction, which reduces the likelihood of significant interaction between DTG and ethinyl estradiol (which is metabolized by CYP enzymes). One study did not find any significant interaction between DTG and a norgestimate/ethinyl estradiol oral contraceptive (122b). Studies of interactions between DTG and progestogen-only contraceptives are underway, but data from these studies are not yet available.

Updates of Section 6, Study Visits and Procedures

12. In Section 6.1, Screening Visits, Procedural Table, Clinical Procedures, first and fourth (added) bullet points:

- Obtain available maternal medical records and maternal medical, ~~and~~ medications, **and contraception history**
- **Assess maternal fertility intentions and willingness to use effective contraceptive postpartum in relation to study requirements**

13. In Section 6.1, Screening Visits, Procedural Table, Laboratory Procedures, third (added), fifth (added), and sixth (added) bullet points:

- **Glucose**
- **Stored whole blood for folate testing**
- **Stored whole blood for HbA1c testing**

14. In Section 6.2, Entry Visit, Procedural Table, Clinical Procedures, first and second (added) bullet points:

- Update medical, ~~and~~ medications, **and contraception history since the last visit***
- **Confirm maternal fertility intentions and willingness to use effective contraceptive postpartum in relation to study requirements***

15. In Section 6.3, Maternal Antepartum Follow-Up Visits, fourth paragraph (added):

Contraception counseling should be provided at each antepartum follow-up visit (see Section 8.6); plans for initiation of effective contraception postpartum should be documented beginning at Antepartum Follow-Up Week 4 and reviewed and updated (if applicable) at each subsequent visit.

16. In Section 6.3.1, Antepartum Follow-Up Week 4 Visit, Procedural Table, Clinical Procedures, first and second (added) bullet points:

- Obtain interval medical, ~~and~~ medications, **and contraception** history
- **Provide contraception counseling and document plan for initiating effective contraception postpartum**

17. In Sections 6.3.2, 6.3.3, and 6.3.4, Antepartum Follow-Up Week 8, Week 12, and Q4 Week Visits, Procedural Tables, first and second (added) bullet points:

- Obtain interval medical, ~~and~~ medications, **and contraception** history
- **Provide contraception counseling and review and update (if applicable) plan for initiating effective contraception postpartum**

18. In Section 6.3.3, Antepartum Follow-Up Week 12 Visit, Procedural Table, Laboratory Procedures, second (added) and fourth (added) bullet points:

- **Glucose**
- **Stored whole blood for HbA1c testing**

19. In Section 6.4, Maternal and Infant Delivery Visit, fourth paragraph (added), fifth paragraph (added), and note (added):

Contraception counseling should be provided at the Delivery Visit (see Section 8.6) and previously-discussed plans for initiation of effective contraception should be finalized at this visit. Effective contraceptive methods are listed in inclusion criterion 4.1.8; IUDs, IUSs, and implantable and injectable hormonal methods are strongly recommended due to their lower failure rates with typical use. Condom use is recommended with all contraceptive methods and counseling should emphasize the importance of condom use during the early postpartum period prior to initiation of effective contraception. Study staff should actively facilitate access to contraceptive services and, to the extent possible, should provide these services on-site.

Mothers choosing contraceptive methods that are clinically appropriate to initiate as of the date of the Delivery Visit should initiate their chosen method at the visit (if not already initiated). Other mothers may return for an additional visit for this purpose. All mothers should initiate effective contraception as soon as feasible and within 27 days after delivery. Because this time frame aligns with the allowable visit window for the Delivery Visit, conduct of a separate visit to initiate contraception within 27 days after delivery will be considered a split Maternal Delivery Visit. Refer to Section 8.6 for more information on management of mothers who do not wish to or are not able to use effective contraception; for any such mothers, DTG must be switched to an alternate ARV, in consultation with the CMC.

Note: For mothers who undergo documented surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy) after delivery or other pregnancy outcome, contraception counseling and initiation of other contraceptive methods are not required thereafter.

20. In Section 6.4, Maternal and Infant Delivery Visit, Maternal Procedural Table, Clinical Procedures, first, second (added), and third (added) bullet points, with footnote (added):

- Obtain interval medical, ~~and~~ medications, **and contraception** history
- **Provide contraception counseling and finalize plan for initiating effective contraception**
- **Initiate effective contraception[†]**

[†]If the Maternal Delivery Visit is split, and the mother returns for an additional visit within the allowable visit window at which effective contraception is initiated, the following should additionally be performed on the day effective contraception is initiated:

- **Obtain interval medical, medications, and contraception history**
- **Provide contraception counseling**
- ***Following counseling and pregnancy testing, initiate effective contraception***
- **Identify/review/update adverse events**
- **Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)**

21. In Section 6.4, Maternal and Infant Delivery Visit, Maternal Procedural Table, Laboratory Procedures, second (added), third (added), seventh (added), and eighth (added) bullet points:

- **Glucose**
- **Hematocrit**
- **Stored whole blood for folate testing**
- **Stored whole blood for HbA1c testing**

22. In Section 6.4, Maternal and Infant Delivery Visit, Infant Procedural Table, Laboratory Procedures, third (added) and fifth (added) bullet points:

- **Glucose**
- **Stored whole blood for folate testing**

23. In Section 6.5, Maternal and Infant Postpartum Follow-Up Visits:

Following delivery, mothers and infants will complete scheduled follow-up visits at 6, 14, 26, 38, and 50 weeks postpartum. For both mothers and infants, the target dates for all postpartum visits are counted from the date of delivery (or other pregnancy outcome) as Day 0. The Week 6 Visit may be conducted within an allowable window of ± 2 weeks. For all other visits, the allowable window is ± 6 weeks. There is no required sequencing of procedures at these visits.

Contraception counseling should be provided at each visit (see Section 8.6); study staff should actively facilitate access to contraceptive services and, to the extent possible, should provide these services on-site. For any mother taking DTG postpartum who reports a desire to

become pregnant, or who does not wish to or is not able to use effective contraception, DTG must be switched to an alternate ARV, in consultation with the CMC.

Note: For mothers who undergo a documented surgical sterilization procedure during postpartum follow-up, contraception counseling and continuation of contraception is not required thereafter.

All infants will undergo HIV testing at Weeks 6, 14, and 50, regardless of feeding method. Breastfed infants will additionally undergo testing at Weeks 26 and 38 ~~if they were exposed to breast milk since the date of their last test~~. In the event of any positive test, the infant should be recalled to the clinic as soon as possible for confirmatory testing. See also Section 6.8.

Maternal creatinine and CrCl evaluations are required at Postpartum Follow-Up Weeks 14, 26, and 50. As soon as the creatinine results from these visits are obtained, the estimated CrCl rate should be calculated using the Cockcroft-Gault formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

24. In all subsections of Section 6.5 and in Sections 6.6 and 6.9, Maternal Procedural Tables for all scheduled Postpartum Follow-Up Visits, Post ARV Switch Visits, and Early Discontinuation Visits, Clinical Procedures, first and second (added) bullet points:

- Obtain interval medical, ~~and~~ medications, **and contraception** history
- **Provide contraception counseling; prescribe and dispense contraception as needed**

25. In Sections 6.5.1, 6.5.2, 6.5.3, 6.5.4, 6.6, 6.7, and 6.9, Maternal Procedural Tables for Postpartum Follow-Up Visits (Weeks 6, 14, 26, and 38), Post ARV Switch Visits, Confirmation of Virologic Failure Visits, and Early Discontinuation Visits, Laboratory Procedures, row added:

Laboratory	Blood or Urine	Collect blood or urine for: <ul style="list-style-type: none"> • Pregnancy test
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26. In Section 6.5.3, Postpartum Follow-Up Week 26 Visit, Infant Procedural Table, Radiology Procedures:

Radiology (<i>at selected sites</i>)	<i>At DXA sites only, for selected participants, DXA scan of whole body and lumbar spine</i>
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27. In Section 6.5.5, Postpartum Follow-Up Week 50 Visit, Maternal Procedural Table, Laboratory and Radiology Procedures:

Laboratory	Blood or Urine	Collect blood or urine for: <ul style="list-style-type: none"> • Pregnancy test (<i>test is required for all mothers; at DXA sites, for selected DXA participants, perform test on same day (preferably) or within 14 days prior to DXA scan</i>) At DXA sites only, collect blood or urine for: <ul style="list-style-type: none"> • Pregnancy test on same day (preferably) or within 14 days prior to DXA scan
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Radiology (<i>at selected sites</i>)	<i>At DXA sites only, for selected participants, DXA scan of lumbar spine and hip</i>
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28. In Section 6.7, Additional Procedures for Confirmation of Maternal Virologic Failure, Procedural Table, Clinical Procedures, first and second (added) bullet points:

- Obtain interval medical, ~~and~~ medications, **and contraception** history (targeted physical exam may be performed if clinically indicated)
- **Provide contraception counseling; prescribe and dispense contraception as needed**

29. In Section 6.11, Maternal Medical, Medications, and Contraception History, section title and first paragraph:

Maternal Medical, ~~and~~ Medications, **and Contraception** History

Collection of medical, ~~and~~ medications, **and contraception** history information is required at each scheduled maternal visit. A baseline history is established at Screening and Entry, and interval (since the last visit) histories are obtained at subsequent follow-up visits. **With respect to contraception history:**

- **Future fertility intentions and willingness to use effective contraception following the current pregnancy will be assessed as part of eligibility determination at Screening and Entry.**
- **Contraception plans will be documented during antepartum follow-up and finalized at the Delivery Visit.**
- **Contraception use will be documented throughout postpartum follow-up.**

All history information may be obtained based on maternal self-report but available medical records should be obtained when possible to supplement self-reported information.

30. Within Section 6.11, Maternal Medical, Medications, and Contraception History, Table 3 title, second column heading, and third row under baseline history elements:

Documentation Requirements for Maternal Medical, and Medications, and Contraception Histories	
Assess for and Source Document	Enter into eCRFs or SES
Reproductive and obstetrical history: <ul style="list-style-type: none"> • Dates and outcomes of all prior pregnancies • Date of last menstrual period prior to the current pregnancy • Medications taken at the time of conception and during the current pregnancy • Complications in the current pregnancy • Other targeted conditions potentially associated with adverse pregnancy outcomes in the current pregnancy • Future fertility intentions and willingness to use effective contraceptive postpartum (following the current pregnancy) 	Yes (all)

31. Within Section 6.11, Maternal Medical, Medications, and Contraception History, Table 3, fourth row, fifth row (added), and sixth row (added) under interval history elements:

Assess for and Source Document	Enter into eCRFs
Use of any new medications since the last visit (see Section 5.8.1 for more information on concomitant medications)	<ul style="list-style-type: none"> • All ARVs taken from time of enrollment through completion of follow-up (including timing of dosing at the Delivery and Week 6 Postpartum Visits) • All medications taken during pregnancy • Postpartum, any new use of: <ul style="list-style-type: none"> – Folate – Cotrimoxazole – Isoniazid prophylaxis – Medications to treat active tuberculosis – Hormonal contraceptives • Postpartum, all medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2 <p>Note: eCRFs will also capture whether corticosteroids were taken for fetal lung maturity at any time during pregnancy.</p>
Contraception plans and use of contraception	<ul style="list-style-type: none"> • All contraceptive methods used through completion of follow-up
Occurrence of subsequent pregnancy	<ul style="list-style-type: none"> • Date of last menstrual period prior to pregnancy • All medications taken at time of conception and during pregnancy • All available fetal ultrasound findings • Pregnancy outcome

32. In Section 6.18.2, Specimen Preparation, Testing, Storage, and Shipping, fourth paragraph:

Most specimens collected and stored at site laboratories per the Schedule of Evaluations are expected to be requested for centralized testing after all participants have completed follow-up (through Week 50 postpartum). However, an interim shipment is planned when all enrolled mothers have delivered. At this time, all specimens stored for centralized HIV-1 RNA testing will be requested for shipment to the designated testing laboratory. These specimens will then be tested as needed to evaluate outcomes through the delivery time point. Interim shipments may also be required for urine samples stored for evaluation of markers of renal toxicity **and whole blood samples stored for evaluation of folate and HgA1c**. Alternative shipping arrangements may be specified by the Protocol Team as needed; detailed shipping instructions will be provided in the LPC.

Updates of Section 7, Safety Assessment, Monitoring, and Reporting

33. In Section 7.2.1, Safety-Related Data Collection for Mothers, listing of adverse events required to be entered into eCRFs, last bullet point:
- All serious adverse events (SAEs) as defined in Version 2.0 of the DAIDS EAE Manual **and all other events that meet criteria for expedited adverse event (EAE) reporting**
34. In Section 7.2.1, Safety-Related Data Collection for Mothers, listing of laboratory test results required to be entered into eCRFs, first (added), third (added), and fourth (added) bullet points:
- **All pregnancy test results**
 - **All glucose results**
 - **All hematocrit results from the Screening and Delivery Visits (required for interpretation of folate test results)**
35. In Section 7.2.2, Safety-Related Data Collection for Infants, listing of laboratory test results required to be entered into eCRFs, second and third bullet points (added):
- **All glucose results**
 - **All hematocrit results from the Delivery Visit (required for interpretation of folate test results)**
36. In Section 7.3.2, EAE Reporting Requirements for this Study, is updated as shown below.

As indicated in Table 5, below, both the SAE (serious adverse event) and SUSAR (suspected unexpected serious adverse reaction) reporting categories, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. ~~The SUSAR category is used for participants in Arm 3, who will be exposed to an approved regimen at approved doses for an approved indication.~~

Any changes of maternal ART regimen will not alter the EAE reporting categories shown in Table 5.

Table 5
Expedited Adverse Event Reporting Requirements for IMPAACT 2010

	Study Entry through Week 14 Postpartum		After Week 14 Postpartum through Study Exit		Study Drugs for which Expedited Reporting is Required
	Mothers	Infants	Mothers	Infants	
Arm 1	SAEs	SAEs	SAEs	SUSARs	DTG, FTC, TAF
Arm 2	SAEs	SAEs	SAEs	SUSARs	DTG, FTC, TDF
Arm 3	SUSARs	SUSARs	SUSARs	SUSARs	EFV, FTC, TDF
Arm 3	SAEs	SAEs	SAEs	SUSARs	EFV, FTC, TDF

~~For mothers in Arm 1 or Arm 2, the EAE reporting categories listed above will be remain unchanged regardless of ART regimen changes. For mothers in Arm 3 who switch to a DTG-containing or TAF-containing regimen, the EAE reporting category will also be switched to the SAE reporting category, from the date of the switch through study exit.~~

~~In addition to the above, the following must also be reported in an expedited manner (i.e., as EAEs) for mothers in Arm 1 or Arm 2 and for mothers in Arm 3 who switch to a DTG-containing or TAF-containing regimen:~~

- ~~• Pregnancy complications that result in medically indicated and/or elective termination of the pregnancy~~
- ~~• Spontaneous abortions and fetal deaths~~

In addition to the above, the following must also be reported in an expedited manner (i.e., as EAEs) for mothers in all arms:

- **Pregnancy complications that result in medically indicated and/or elective termination of the pregnancy**
- **Spontaneous abortions and fetal deaths**
- Hepatic toxicities that result in discontinuation of DTG or EFV
- Serious ABC hypersensitivity reactions in mothers switching from TDF or TAF to ABC

Updates of Section 8, Participant Management

37. In Section 8.6, Contraception and Management of Mothers who Become Pregnant on Study, is updated as shown below:

8.6.1 Contraception Counseling and Provision

The WHO advises that “At least two years between giving birth and the next pregnancy is healthy for both mother and child” (122c). Mothers enrolled in this study will be provided with contraception counseling throughout antepartum and postpartum follow-up. Mothers will be informed of available contraceptive methods and counseled to initiate effective contraception as soon as appropriate after delivery. IUDs, IUSs, and implantable and injectable hormonal methods are strongly recommended due to their lower failure rates with typical use; mothers should be encouraged to use one of these methods. Male or female condom use will be recommended with all contraceptive methods for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections; the importance of condom use will be emphasized during the early postpartum period prior to initiation of effective contraception. Mothers will be informed of the benefits of folate intake for a healthy pregnancy and advised to take folate supplements and/or eat folate-rich foods.

Fertility intentions and willingness to use effective contraception postpartum will be documented at the Screening and Entry Visits as part of eligibility determination for the study. Contraception counseling will be provided to enrolled mothers at each antepartum follow-up visit; plans for initiating effective contraception postpartum will be documented beginning at the Antepartum Week 4 Visit; and these plans will be reviewed and updated (if applicable) at each subsequent antepartum visit. At the Delivery Visit, previously-discussed plans will be reviewed, further counseling will be provided, and plans for initiating effective contraception will be finalized. Mothers choosing contraceptive methods that are clinically appropriate to initiate as of the date of the Delivery Visit will ideally initiate their chosen method at the Delivery Visit (if not already initiated). Other mothers will complete an additional visit within 27 days after

delivery at which initiation should occur. Contraception counseling will then continue throughout postpartum follow-up, unless a mother undergoes a documented surgical sterilization procedure, after which counseling may be discontinued.

Contraception counseling will be provided per site SOPs, which should reflect study-specific requirements, locally available contraceptive methods, and site-specific plans for provision of contraceptive methods to study participants. The benefits of child spacing for maternal and child health will be emphasized to all mothers, and the importance of avoiding pregnancy while on DTG will be further emphasized to mothers taking DTG postpartum. While mothers in all study arms will be provided with contraception counseling and access to contraceptive services, use of effective contraception is most important for mothers taking DTG postpartum.

Study staff should actively facilitate access to contraceptive services and, to the extent possible, should provide these services to study participants on-site. At sites where full service provision is not possible, study staff should actively refer participants to local service providers for methods that cannot be provided on site. Access to effective contraception should be provided or facilitated for all mothers, regardless of study arm and ART regimen. The benefits of long-acting reversible methods compared to other methods — including higher effectiveness with typical use — should be emphasized to all mothers. A long-acting reversible method (IUD, IUS, or implantable or injectable hormonal method) should be strongly recommended to mothers taking DTG whenever possible.

Potential interactions with other medications, including but not limited to ARVs, should be considered when selecting a contraceptive method. For example, the efficacy of combined oral contraceptives and progestin-containing subdermal implants appears to be decreased when used in combination with EFV. For women who will be breastfeeding, IUDs, IUSs, and progestin-only implants and injections can be started shortly after delivery.

Regardless of the contraception counseling and access to effective contraception provided or facilitated by study staff, some mothers may decline or stop use of effective contraception. This is acceptable; each mother's choices should be accepted and will have no impact on her continued study participation. Mothers should be supported in open and honest reporting of their pregnancy intentions and adherence to contraceptive use, with active reminders that their continued participation in the study will not be affected by their choice of contraceptive method or their adherence to their chosen method. Mothers should also be reminded to inform study staff if they wish to become pregnant, miss a dose of contraception, or suspect they may be pregnant, again with no impact on their continued participation in the study. However, for any mother taking DTG postpartum who reports a desire to become pregnant or who does not wish to or is not able to use effective contraception (as listed in criterion 4.1.8), DTG must be switched to an alternate ARV, in consultation with the CMC.

~~Mothers should be provided with contraception counseling as needed during their participation in the study. Counseling should be provided per site SOPs, which should reflect WHO guidelines for HIV-infected women as well as local standards of care. Counseling should begin during pregnancy and continue postpartum as needed for each mother, and should reflect the ARVs that mothers are currently taking and the potential interactions between these ARVs and available contraceptive methods. Study sites should ideally~~

~~integrate provision of contraceptive methods with other services offered to study participants and should provide referrals to non-study sources of methods that cannot be provided at the study site.~~

8.6.2 Management of Mothers who Become Pregnant on Study

Pregnancy testing is **required at each scheduled postpartum study visit following the Delivery Visit** and ~~not required per the study Schedule of Evaluations~~. Nonetheless, testing may **additionally** be performed when clinically indicated at any time during **postpartum** maternal follow-up. **Mothers should be instructed to contact study staff as soon as possible if they suspect they may be pregnant at any time during postpartum follow-up, so that an interim pregnancy test can be performed between scheduled visits if indicated.**

Mothers who become pregnant will be maintained in follow-up ~~and may remain on their current ART regimen during the new pregnancy~~. When the new pregnancy is identified, mothers will be provided information and counseling on their current **ART** regimen and what is known about the safety of the ARVs that comprise the regimen during pregnancy. Mothers who **conceive while taking DTG will be switched from DTG to an alternate ARV if still in the first trimester when the pregnancy is identified; if the pregnancy is identified after the first trimester, mothers taking DTG may choose to continue their current regimen** ~~wish to change regimens based on this counseling will be permitted to do so, and~~. Site clinicians ~~should~~ **may** consult with the CMC regarding any mothers **who conceive while taking DTG and any other mothers** for whom a regimen change may be clinically indicated or otherwise considered in the best interest of the mother or fetus. For any mother whose study drug regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6. Mothers who choose to receive study drug during a subsequent pregnancy must provide separate informed consent to do so (refer to Section 12.3 and Appendix V).

Mothers who become pregnant on study should be offered a referral for a fetal ultrasound scan between 14 and 22 weeks gestation. The scan should confirm the dating of the pregnancy and evaluate fetal anatomy; results should be entered into eCRFs. To provide optimal assessment of fetal anatomy, it is preferable for this scan to be performed between 18 and 22 weeks gestation; however, the scan can be performed as early as 14 weeks gestation if necessary. Mothers may choose to undergo or decline this scan, after discussion with study staff.

All pregnancies and pregnancy outcomes should be ascertained and entered into eCRFs. For mothers who are pregnant at the time of study exit, additional post-study contacts should be completed to ascertain their pregnancy outcomes as well as any ART regimen changes after study exit (see Section 6.10). These data may be ascertained based on maternal report but medical records should be obtained whenever possible to supplement maternal reports.

Study sites are strongly encouraged to prospectively register participants with subsequent pregnancies in the Antiretroviral Pregnancy Registry (APR) prior to pregnancy outcome by calling the following number in the US: +1-800-258-4263. Outside of the US, please see the APR website (www.apregistry.com) for additional toll-free numbers.

Updates of Section 9, Statistical Considerations

38. In Section 9.2.3, table row added for Section 9.2.3.7:

9.2.3.7	<ul style="list-style-type: none">• Maternal folate, glucose, and HbA1c• Infant folate and glucose
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39. In Section 9.6.3, Exploratory Outcome Analyses, second paragraph:

The DTG-containing arms will be compared to the EFV-containing arm for the maternal postpartum depression score, **folate, glucose, and HbA1c** using a two-sample t-test to test the equality of means. **Similarly, infant folate and glucose will be compared between the DTG-containing arms and the EFV-containing arm using a two-sample t-test.**

40. In Section 9.6.3, Exploratory Outcome Analyses, fourth paragraph:

Generalized linear models and Cox regression models will be used to investigate immunologic and hormonal predictors of adverse pregnancy outcomes and postpartum maternal health outcomes while adjusting for potential confounders. **Maternal and infant folate and glucose and maternal HbA1c will be analyzed in a similar manner.**

Updates of Section 12, Human Subjects Protections

41. In Section 12.5, Potential Risks, fourth paragraph:

Please refer to Section 1.2-1.8 and the Package Inserts for the study drugs for a complete description of the potential risks associated with use of these drugs. **DTG taken at the time of conception or very early pregnancy may be associated with NTDs in the fetus. There is no evidence that the risk of NTDs or other birth defects is increased when DTG is started after the early first trimester of pregnancy. Every effort will be made in this study to avoid the occurrence of new pregnancies among mothers taking DTG.**

Updates of Section 15, References

42. The following references were added in Section 15:

- 12a. **Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLOS ONE. 2016;11(10):e0162775.**
- 12b. **Joint United Nations Programme on HIV/AIDS (UNAIDS). Global AIDS Monitoring 2018: Indicators for monitoring the 2016 United Nations Political Declaration on Ending AIDS. Geneva: 2018 [cited 30 May 2018]. Available from: http://www.unaids.org/sites/default/files/media_asset/global-aids-monitoring_en.pdf.**
- 12c. **HIV Treatment and Care: Treat All: Policy Adoption and Implementation Status in Countries [fact sheet]. Geneva: World Health Organization Department of HIV/AIDS. 2017 [cited 30 May 2018]. Available from: <http://apps.who.int/iris/bitstream/handle/10665/259532/WHO-HIV-2017.58-eng.pdf?sequence=1>.**

- 27a. Shapiro R. Birth Outcomes Surveillance in Botswana. RO1 from United States National Institutes of Health (Project Number 5R01HD080471-05). Available from: https://projectreporter.nih.gov/project_info_details.cfm?aid=9481292&icde=39703357
- 27b. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex M, et al. Comparative Safety of Antiretroviral Treatment Regimens in Pregnancy. *JAMA Pediatr.* 2017;171(10):e172222.
- 27c. World Health Organization Statement on DTG: Potential safety issue affecting women living with HIV using dolutegravir at the time of conception [press release]. Geneva, 18 May 2018 [cited 31 May 2018]. Available from: <http://www.who.int/hiv/mediacentre/news/dtg-statement/en/>.
- 27d. Shapiro R, Zash R. Personal communication. May 2018.
- 27e. Mofenson L. Personal communication. May 2018.
- 27f. Padmanabhan R. Etiology, pathogenesis and prevention of neural tube defects. *Congenital Anomalies.* 2006;46(2):55-67.
- 27g. Parnell AS, Correa A, Reece EA. Pre-pregnancy Obesity as a Modifier of Gestational Diabetes and Birth Defects Associations: A Systematic Review. *Maternal and Child Health Journal.* 2017;21(5):1105-20.
- 122a. Nanda K, Stuart GS, Robinson J, Gray AL, Tepper NK, Gaffield ME. Drug interactions between hormonal contraceptives and antiretrovirals. *AIDS.* 2017;31(7):917-52.
- 122b. Song IH, Borland J, Chen S, Wajima T, Peppercorn AF, Piscitelli SC. Dolutegravir has no effect on the pharmacokinetics of oral contraceptives with norgestimate and ethinyl estradiol. *Annals of Pharmacotherapy.* 2015;49(7):784-9.
- 122c. World Health Organization Department of Reproductive Health and Research (WHO/RHR) and Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP) Knowledge for Health Project. *Family Planning: A Global Handbook for Providers (2018 update)*. Baltimore and Geneva: CCP and WHO, 2018. Available from: <http://www.who.int/reproductivehealth/publications/fp-global-handbook/en/>

Updates of Appendix I, Schedule of Evaluations

43. Consistent with the updates in protocol Section 6, and for ease of reference and implementation, the Schedule of Evaluations is updated as shown (with revisions incorporated) on pages 24-27 of this LoA.

Updates of Appendix III, Sample Informed Consent Form

44. In Item 4, “We will ask you questions, examine you, and discuss the study requirements with you,” fourth bullet point:
 - Talk with you about the study requirements and if you are able to meet the requirements. **This will include talking about your plans for having more children in the future.**
45. In Item 7, “If you and your baby qualify, you will enter the study within 2 weeks of your first visit,” second bullet point (added):
 - **Ask about your plans for having more children in the future.**

46. In Item 9, “Mothers will have visits every 4 weeks while pregnant,” third bullet point (added):

- **Talk with you about family planning and the methods of family planning you would like to use after your pregnancy. There are certain methods specified to be used in this study. Different methods may be required depending on the ARVs you are taking. We will tell you about the methods and help you choose the best method for you.**

47. In Item 10, “Mothers and babies will have a visit soon after delivery. Then they will have 5 more visits over 1 year,” first and second (added) paragraph:

We will stay in contact with you as you get close to your delivery date. We will ask you to contact us when your labor begins. We will arrange for your first mother-baby visit as soon as possible after delivery. It is important for this visit to take place close to the baby’s birth. At the latest, the visit **should** ~~must~~ be within 14 days of the baby’s birth. This visit will take up to 4 hours.

We will talk with you again about family planning and help you with starting your chosen method. We may ask you to return on another day to start your chosen method. Your chosen method should be started within the first month after delivery. If you do not use family planning, you may be required to change the ARVs you are taking. See also #13a (below).

48. In Item 10, “Mothers and babies will have a visit soon after delivery. Then they will have 5 more visits over 1 year,” under “For mothers, we also will,” second (added) bullet point and added paragraph following bulleted list:

- **Draw blood (1 mL or a few drops) or collect urine (5 mL or about 1 teaspoon) for a pregnancy test.**

[...]

We will talk with you about family planning at each visit. We will ask you to tell us right away if you wish to become pregnant again or if you think you may be pregnant. We will give you family planning or tell you where you can go for family planning as needed. See also #13a (below).

49. Item 12, “Mothers will have extra visits if their ARVs are changed or if their HIV is not controlled,” paragraph added following bulleted list:

We will also talk with you about family planning. We will ask you to tell us right away if you wish to become pregnant again or if you think you may be pregnant. We will give you family planning or tell you where you can go for family planning as needed. See also #13a (below).

50. Item 13a, “Mothers should not become pregnant again while taking DTG,” (added):

13a. Mothers should not become pregnant again while taking DTG.

We will talk with you about family planning at each visit. After delivery, if you wish to become pregnant again, or think you may be pregnant, please tell us right away. We will test your blood or urine to find out if you are pregnant.

If you are taking DTG, you should not become pregnant again while taking DTG. This is because taking DTG at the time of becoming pregnant may increase the risk of serious birth defects of the brain or spine in the new baby. For this reason, you will be required to use family planning if you are taking DTG. We will tell you about the methods that must be used. If you wish to become pregnant again, or do not wish to use the required family planning methods, you will stop taking DTG. We will give you other ARVs to take instead of DTG. This will have no effect on your staying in the study. You and your baby will stay in the study as originally planned.

51. For Item 14, “Mothers who become pregnant again may have extra procedures,” first paragraph (deleted):

~~Mothers could become pregnant again while in the study. We will talk with you about family planning. If you wish to become pregnant again, or think you may be pregnant, please tell us right away. We will test your blood or urine to find out if you are pregnant.~~

52. For Item 14, “Mothers who become pregnant again may have extra procedures,” third paragraph (added):

The study can offer an ultrasound scan of your new baby when you are 14 to 22 weeks pregnant. It is your choice whether or not to have the scan. There will be no cost to you for transport or having the scan done.

53. For Item 16, “We may change or stop your ARVs,” first paragraph:

At all of your visits, we will check whether the ARVs you are taking may be causing bad effects. If so, the ARVs may be changed or stopped. The ARVs may be changed if you have certain illnesses or need to take other medicines that cannot be taken with ARVs. **DTG may be changed if you do not use family planning, or if you become pregnant again while taking DTG.** We will always discuss ARV changes with you. Please tell us about any problems you may have with taking your ARVs.

54. For Item 24, “There are other possible risks from ARVs,” Possible effects on pregnancy, unborn babies, and breastfeeding babies, third paragraph:

In this study, ARVs are given after the first 3 months of pregnancy. The ARVs are continued through pregnancy and after delivery. After delivery, mothers who become pregnant again may be taking ARVs during the first 3 months of their new pregnancy. If you become pregnant again, we will talk with you about your choices for taking ARVs during your new pregnancy (see also #14 above). **Early results from a large study in Botswana showed that DTG may increase the risk of serious birth defects of the brain or spine in the new baby. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.**

55. On the Signatures page:

If you decide to join this study with your baby, sign or make your mark below.

Before deciding whether to join this study with your baby, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your baby if you decide to join.

Your signature or mark on this form means you understand the study and have decided to join with your baby. It also means you:

- **Understand the potential risk of becoming pregnant again while taking DTG**
- **Understand the importance of using family planning after your baby is born**

We will tell you any new information from this study or other studies that may affect your willingness for you and your baby to stay in the study. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

Updates of Appendix V, Sample Informed Consent Form for Use of Study Drug during Subsequent Pregnancy

56. In Item 3, “The risks and benefits of taking ARVs from the study in your new pregnancy are the same as in your previous pregnancy,” title and section:

The risks and benefits of taking ARVs from the study in your new pregnancy **may not be** ~~are~~ the same as in your previous pregnancy.

In your previous pregnancy (when you first joined the study), you started taking ARVs 3 or more months after you became pregnant. For this new pregnancy, you have been taking ARVs since you first became pregnant. Because of this, the risks and benefits of the ARVs may be different in your new pregnancy.

The ARV called dolutegravir (DTG) may increase the risk of serious birth defects of the brain or spine in the new baby, if taken at the time of becoming pregnant or early in pregnancy. For this reason, if you learn of your new pregnancy within the first 3 months, you will stop taking DTG. If you learn of your new pregnancy later than that, you can keep taking DTG. This is because these defects happen in the first 4 weeks of pregnancy.

~~If you are past the first three months in your new pregnancy, there is no change in the possible risks and benefits of taking ARVs from the study now compared to when you first joined the study. If you are in the first three months, it is possible that the risks and benefits could be different. We do not yet know much about this at this time.~~

We will ~~tell you review~~ what is known about the risks and benefits **of all the ARVs you are taking with you**. If any new information about the risks and benefits becomes available later, we will give you that information and again discuss your choice of ARVs. You can ask questions or request more information at any time. **We will help you choose the ARVs that are best for you.**

57. In Item 6, “The study cannot provide medical care for your new pregnancy,” first paragraph (added):

The study can offer an ultrasound scan of your new baby when you are 14 to 22 weeks pregnant. It is your choice whether or not to have the scan. There will be no cost to you for transport or having the scan done.

The study cannot provide medical care related to your new pregnancy or delivery of a new baby. If you have another baby, that baby will not be in the study. Therefore, it is important for you to receive medical care related to your pregnancy outside the study. We will tell you where you can go for this care. *[Sites may modify or add to the preceding sentence to provide site-specific details on provision and/or referral for care.]*

Appendix I Schedule of Evaluations
Antepartum

Study Visit	Screen	Entry	Weeks During Pregnancy				Post ARV Switch ²	Early D/C ³
			Week 4	Week 8	Week 12	Q4 Weeks ¹		
Visit Window	up to -14 d	Day 0	±2 wks	±2 wks	±2 wks	±2 wks		
MATERNAL EVALUATIONS								
Informed consent	X							
Maternal medical, medications, and contraception history	X	X	X	X	X	X	X	X
ARV adherence questionnaire ⁴			X	X	X	X	X	X
Sleep and anxiety questionnaires		X		X			X	
Depression questionnaire							X	
Physical examination	X	X	X	X	X	X	X	X
Fetal ultrasound	prior to or within 14 days after entry							
Confirmatory pregnancy testing ⁵	X							
Confirmatory HIV testing	0-6 mL							
Hepatitis B surface antigen		3 mL						
AST, ALT, creatinine, CrCl	4 mL		4 mL		4 mL	4 mL Wk 24	4 mL	4 mL
Glucose	X*				X*			
Complete blood count	3 mL							
CD4+ cell count		3 mL						
HIV-1 RNA (store residual plasma) ⁶		6 mL	6 mL	6 mL	6 mL	6 mL Wk 24 ⁶	6 mL	6 mL
Stored whole blood	X*				X*			
Stored plasma	6 mL							
Stored plasma and cell pellets		10 mL		10 mL				
Stored urine		15 mL						15 mL
Total blood volume	13-20 mL	22 mL	10 mL	16 mL	10 mL	0-10 mL	10 mL	10 mL

Appendix I Antepartum Footnotes:

*For these evaluations, the required blood volume will be obtained from other collected specimens; refer to the LPC for detailed specimen collection and processing instructions.

¹Refer to Section 6.3.4. After antepartum study Week 12, mothers will complete scheduled follow-up visits every four weeks (Q4) prior to delivery. Depending on the date of delivery, these visits may take place at antepartum study Weeks 16, 20, 24, and 28.

²Refer to Section 6.6.

³Refer to Section 6.9.

⁴Routine questionnaire at all indicated visits; barriers and facilitators questionnaires at Antepartum Week 8.

⁵Refer to Section 6.1. If available medical records document a positive pregnancy test result, or if pregnancy is confirmed by ultrasound scan prior to entry, no pregnancy testing is required. Otherwise, a blood (1 mL) or urine (5 mL) pregnancy test should be performed, with results available for final eligibility determination prior to entry. The total blood volume shown in the Screen column above accommodates collection of 1 mL of blood if needed.

⁶It is generally not expected that mothers will meet the criteria for confirmation of virologic failure (≥ 200 copies/mL at or after at least 24 weeks on study) during antepartum follow-up; however, if these criteria are met prior to delivery, the Confirmation of Virologic Failure evaluations shown on the next page and further described in Section 6.7 should be performed.

**Appendix I Schedule of Evaluations
Delivery and Postpartum**

	Delivery	Weeks Postpartum					Post ARV Switch ¹	Confirmation of Virologic Failure ²	Early D/C ³
	up to 14/27 d [†]	6	14	26	38	50			
<i>Study Visit</i>									
<i>Visit Window</i>	<i>New Day 0</i>	± 2 wks	± 6 wks	± 6 wks	± 6 wks	± 6 wks			
MATERNAL EVALUATIONS									
Maternal medical, medications, and contraception history	X	X	X	X	X	X	X	X	X
ARV adherence questionnaire ⁴	X	X	X	X	X	X	X	X	X
Sleep and anxiety questionnaires					X		X		
Depression questionnaire		X				X	X		
Physical examination	X	X	X	X	X	X	X	[X]	X
Pregnancy test ⁵	[X]	X	X	X	X	X	X	X	X
AST, ALT, creatinine, CrCl	4 mL		4 mL	4 mL		4 mL	4 mL		4 mL
Glucose	X*								
Complete blood count				3 mL		3 mL			
CD4+ cell count				3 mL		3 mL			
HIV-1 RNA (store residual plasma)	6 mL		6 mL	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL
ARV resistance testing (store residual plasma)								6 mL	
Stored whole blood	X*								
Stored plasma	6 mL	6 mL							
Stored plasma and cell pellets	10 mL					10 mL			
Stored serum ⁶	0-4 mL ⁶								
Stored breast milk (if breastfeeding)		20 mL							
Stored urine						15 mL			15 mL
Stored hair	X								
DXA scan (at selected sites) ⁷						X ⁷			
Total blood volume	26-31 mL	7 mL	11 mL	17 mL	7 mL	27 mL	11 mL	13 mL	11 mL

Appendix I Schedule of Evaluations Delivery and Postpartum

	Delivery	Weeks Postpartum					Post ARV Switch ¹	Confirmation of Virologic Failure ²	Early D/C ³
	up to 14/27 d [†]	6	14	26	38	50			
Study Visit									
Visit Window	New Day 0	±2 wks	±6 wks	±6 wks	±6 wks	±6 wks			
INFANT EVALUATIONS									
Infant medical and feeding history	X	X	X	X	X	X			X
Physical examination	X	X	X	X	X	X			X
HIV NAT (store remnant samples) ^{8,9}	3 mL	4 mL ⁹	3 mL	3 mL if BF	3 mL if BF	3 mL			3 mL
ALT and creatinine ¹⁰	1 mL			1 mL if BF					
Glucose	X*								
Complete blood count ¹⁰	1 mL			1 mL if BF					
Stored whole blood	X*								
Stored serum ⁶	0-1 mL ⁶								
Stored hair	X								
DXA scan (at selected sites)				X					
Total blood volume	5-6 mL	4 mL	3 mL	0-5 mL	0-3 mL	3 mL			3 mL

[†]The Delivery Visit should be conducted as soon as possible after delivery and within a targeted window of 14 days after delivery. If the visit cannot be conducted within the targeted window, it may be conducted within an allowable window of 27 days after delivery. The timeliness of visit completion at each site will be closely monitored and corrective actions taken when needed, as described in Sections 6.4 and 9.5.1.

*For these evaluations, the required blood volume will be obtained from other collected specimens; refer to the LPC for detailed specimen collection and processing instructions.

¹Refer to Section 6.6.

²Refer to Sections 6.7 and 8.3.

³Refer to Section 6.9.

⁴Routine questionnaire at all indicated visits; barriers and facilitators questionnaires at Postpartum Week 38.

⁵Refer to Section 6.4 for pregnancy testing requirements at the Delivery Visit (testing may be required if a split visit conducted). At visits following the Delivery Visit, a blood (1 mL) or urine (5 mL) pregnancy test must be performed at each scheduled visit. The total blood volume shown in each column accommodates collection of 1 mL of blood if needed.

⁶At Delivery, collect maternal and infant blood for serum storage only if the mother is at risk for Zika virus infection (due to local transmission, travel, or other exposure) and maternal Zika virus infection during the current pregnancy is suspected.

⁷Maternal DXA scan must be preceded by a pregnancy test, either on the day of the scan (preferably) or within 14 days prior to the scan.

⁸For infants ever exposed to breast milk, perform HIV NAT at Delivery and Weeks 6, 14, 26, 38, and 50. For infants never exposed to breast milk, perform HIV NAT at Delivery and Weeks 6, 14, and 50. Also refer to Section 6.8. Any infant with an initial positive HIV NAT result should be recalled to the clinic as soon as possible for confirmatory testing.

⁹At Week 6, 4 mL is required to provide sufficient plasma for HIV NAT and testing of ARV drug levels.

¹⁰At Week 26, perform testing (ALT, creatinine, complete blood count) for infants ever exposed to breast milk.